# inflammation implication

## how our aging immune system goes haywire

Danger stalks the body from without and within. For most of human evolution, the biggest killers have been foreign invaders — not other humans, but the microbial pathogens that mosquitoes inject into us (malaria, dengue, yellow fever) as well as countless other variously transmitted bacterial and viral pests.

**But the gears have shifted.** Medical and public-health advances have so vastly reduced the death toll from microbes that today's leading killers spring from within. People are living long enough to acquire debilitating bug-free disorders such as heart disease, strokes, cancer, osteoarthritis, Type 2 diabetes and neurodegenerative syndromes such as Alzheimer's.

A common element in all of these appears to be inflammation — not the intense, temporary, ad hoc (or, as immunologists say, acute) variety that's actually helpful when you run a fever while you're fighting off an infection, but another kind that's stealthy, steady and pernicious, like a leaky faucet. It doesn't seem like a big deal until the water bill comes.

With advancing age, there's an escalating tendency for our immune system to go haywire. It becomes less capable of protecting us against infections and cancer or responding to vaccinations but, paradoxically, increasingly prone to wallowing in a state of vague, nonspecific irritation that's called chronic low-grade inflammation.

Along with this progression — which immunologists have dubbed "inflammaging" — comes a growing vulnerability to disease.

If we knew why and how inflammaging occurs, we might be able to find ways to forestall or override it. For example, researchers at Stanford and elsewhere are gaining deeper insights into the inflammatory underpinnings of the world's No. 1 killer, cardiovascular disease, leading to studies testing new treatments. Two huge national trials are now exploring whether anti-inflammatory medications used by patients with autoimmune diseases can prevent heart attacks and strokes.

Similar insights and ideas for treatments are emerging for other diseases of aging, too.

BY BRUCE GOLDMAN

ILLUSTRATION BY MARK SMITH

## THE TWO ARMS OF THE IMMUNE SYSTEM

Many scientists theorize that a big factor in inflammaging, and the susceptibility to many diseases that comes with it, is that one of the immune system's two arms — the "adaptive" immune system — is increasingly tied behind its back, leaving the other arm — the "innate" immune system — to pick up the slack.

We don't hear that much about the innate immune system, which is present even in such evolutionary ancient organisms as sponges. We moderns couldn't live without it, either. This arm of the immune system is fast and powerful, but hasty and somewhat indiscriminate.

We've perhaps heard more about the immune system's slower to respond, but far more targeted, other arm: the adaptive immune system, which evolution has installed in us vertebrates to provide highly selective protection against infections and cancer while sparing healthy tissues. The adaptive immune system consists mainly of cells called lymphocytes.

Stated loosely, any given lymphocyte is narrowly focused on a particular biochemical shape or, in science-ese, "antigen." Recognizing this specific antigen on a tumor cell or pathogen or in a vaccine, the lymphocyte proceeds to undergo round upon vigorous round of rapid-fire replication. But that lymphocyte will proliferate only in response to the antigen to whose shape it's attuned.

"A healthy young adult's body harbors billions of lymphocytes that, in the aggregate, can recognize 100 million different antigens," says Jorg Goronzy, MD, professor of medicine, whose career has focused on the aging immune system. "But typically only a handful of those billions of lymphocytes are geared to respond to any given antigen." When a pathogen appears on the scene, this handful has to turn into an army, meaning lymphocytes have to divide like crazy. It takes them days or weeks to fire up to full fighting strength.

"If you had to wait that long to be able to take on a pathogen, you'd be dead," Goronzy says.

But you don't. The innate immune system's various constituent cell types all feature, both internally and on their surfaces, families of "pattern recognition" receptors that sense broad, generic signs of infection and injury: for instance, material smacking of bacterial cell walls, or DNA bearing telltale microbial sequences. These abundant, one-size-fits-all fighter cells can quickly sense the presence of a virus or bacterium and, without bothering to distinguish among the millions of varieties of each or needing to proliferate, respond swiftly, fiercely and wantonly, often inflicting collateral damage on healthy tissue.

That can spell trouble.

> IT'S NOT JUST A SINGLE INVISIBLE HAND STEADILY TURNING UP THE INFLAMMATORY DIAL AS THE YEARS GO BY, BUT MANY.

## SLOWLY SIMMERING

It's not just a single invisible hand steadily turning up the inflammatory dial as the years go by, but many.

Like our closets, our bodies accumulate junk as we age. Garbage that can't be metabolized piles up within aging cells or gets sloughed off alongside them. One job of innate immune cells known as macrophages (derived from the Greek words for "big" and "eater") is to ingest and metabolize all that garbage, preventing dead and dying cells from throwing off inflammation-promoting substances. But macrophages' garbage-gobbling gumption declines with age.

Meanwhile, chronic viral infections we accumulate — cytomegalovirus, Epstein-Barr virus, herpesviruses — are constantly challenging the immune system to a fight. Bacteria, trillions of which happily inhabit our intestines (where they usually do us much more good than harm) poke through our older, and therefore leakier, gut linings into the circulation, angering our innate immune system, which doesn't know them and doesn't like them. The body becomes an increasingly pro-inflammatory environment.

As we get older, our adaptive immune system gradually goes to seed. We end up with not enough different kinds of lymphocytes, and too many of some of the kinds that we do have. Every battle against a microbial foe or incipient tumor leaves behind milling masses of surplus immune warrior cells with time on their hands. That can foster autoimmune disease. A team led by Cornelia Weyand, MD, professor of medicine and chief of that department's division of immunology and rheumatology, has identified a kind of lymphocyte whose job it is to keep other lymphocytes in check. This regulatory lymphocyte acts as a sort of military policeman that quiets down the adaptive immune system after it has been, however justifiably, in a state of battle readiness. With time, this class of regulatory lymphocytes begins to fail, leaving us with continuous, simmering inflammation. Weyand's group has tied deficits in these cells' capacity to do their policing to the likelihood and se-

## WHAT CAN WE DO?

**While researchers sort out** the factors that lead low-grade chronic inflammation to increase as we age, there may be steps we can take on our own to slow it down.

For example, it may pay to watch your waistline. A potbelly in some respects resembles a huge gland capable of secreting inflammation-producing proteins into the circulation. That's because fat cells are notoriously capable of releasing hormones and other chemicals like IL-6 and TNF-alpha, which drive potentially aggressive immune cells called macrophages wild. And belly fat is loaded with shocking numbers of macrophages. Plus, the pattern-recognition receptors that are the primary initiators of the inflammatory response can, during particularly inflammatory times, sprout on fat cells, too. The chronic low-grade inflammation and macrophage infiltration typifying belly fat have been linked to both Type 2 diabetes and cardiovascular disease.

**Vaccinations are another smart bet.** "We think vaccination is one of the best interventions we have to prevent immune aging," says Cornelia Weyand, MD, professor and chief of immunology and rheumatology at Stanford. "Every time we have an infection, we pay a price. The more we can keep the immune system from being called into action, the better we can preserve it."

**Finally, your grandma** was right about dietary fiber — which essentially translates to "complex carbohydrates we can't digest but our gut-dwelling microbes can." Justin Sonnenburg, PhD, associate professor of microbiology and immunology, has found evidence that a lack of fiber in the diet may be, among other things, forcing our gut-resident microbes to subsist by scavenging sugar molecules from the long strings of them composing the mucus layer that lines our gut. The consequent thinning of the intestinal barrier, he thinks, may provide a portal allowing gut microbes to break out into the bloodstream, helping to induce a simmering inflammatory environment.

"Good fences make good neighbors," he says.

verity of strongly age-related autoimmune diseases such as giant-cell arteritis, a condition affecting one in 500 older people but never seen in people under age 50. The team is now analyzing blood from patients with cardiovascular disease to see if similar regulatory lymphocyte deficits play a major part in that far more common condition, as well. (Preliminary evidence suggests this may be the case, Weyand says.)

Meanwhile, as we age, it's harder for the adaptive immune system to respond to novel pathogens. Our remaining lymphocytes — having encountered life's continuing barrage of troubles — are increasingly dedicated to recognizing and responding to specific "remembered" antigens they've previously encountered, and less flexible in their aggregate ability to recognize and respond to novel antigens that characterize new tumor cells or pathogens. Also, lymphocytes in this jaded, battle-hardened state are more prone to spontaneously secrete inflammatory factors than when in their "naïve" state.

In short, there are many ways for people's immune systems to go astray with age.

### A CASE IN POINT

Between a quarter and a third of all deaths in the United States are traceable to impaired flow of oxygen-rich blood to the heart (coronary heart disease) or the brain (stroke). The underlying process, atherosclerosis — the gradual buildup of plaques in our arteries — was once thought to be the simple result of eating too much fat, which was believed to coat the insides of our arteries and congeal into plaques that thicken over time, impeding circulation.

"But you don't just gradually have circulatory shrinkage until you finally gasp for breath," says Weyand. "Heart attacks and strokes occur all of a sudden. Why?"

Fatty substances are indeed a prime constituent of an arterial plaque, but there's more than fat deposition going on there. For one thing, plaques are stuffed with a variety of dead or near-dead smooth-muscle and endothelial cells associated with blood-vessel walls.

Those plaques also contain lots of immune cells — chiefly macrophages, those "big eaters" that devour invading bacteria, debris and dead cells left behind after injury or infection.

Mature macrophages generally assume one of two personae. The gentler ones, called M2 macrophages, nibble dead cells and extracellular detritus, releasing healing factors that encourage new cell growth and stimulate blood flow, and otherwise overseeing tissue repair.

"Our body turns over more than 100 billion cells per day, every day," says Nicholas Leeper, MD, associate professor of vascular surgery and of cardiovascular medicine. "Those cells all need to be cleared before they undergo a kind of death in which they release inflammatory material." All hail the M2 macrophages.

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ery." Menus should tell the right stories about healthy items; it's not a matter of disguising what's in a dish, but rather of talking about it in a way that will appeal primarily to customers' taste instead of scolding them into doing what's good for them. "A great majority of Americans are way more open to culinary adventure than they once were," Drescher says. Chefs can take advantage by presenting their creations as mini-vacations to interesting locales.

One healthy-cooking technique the collaborators are studying, dubbed "the flip," changes what's at the center of the plate. It seeks a middle ground between huge, carnivore-sating portions of meat and none at all. "We can say, 'But it's not vegetarian! This salad has steak in it; it's global cuisine; we're going for flavor profile,'" Gardner says. Behind the scenes, the health justification for the change is grounded by epidemiological data linking high consumption of red meat and processed meat with obesity, Type 2 diabetes, cardiovascular disease and some forms of cancer, as well as evidence that diets high in vegetables and fruits protect against several chronic diseases.

To help convince chefs that the "protein flip" would work, Drescher and his team collected data on what happened when they replaced some meat in hamburger patties with ground sautéed mushrooms. "We started to make prototypes and said, wow, this is really good," Drescher says. He enlisted a food science team at the University of California-Davis to analyze whether the flavor stood up to traditional all-beef mixtures. The results, published in the *Journal of Food Science* in 2014, were convincing: Adding mushrooms boosts flavor with less sodium, less fat and fewer calories. It solves other problems, too.

"In volume food service, you can't serve medium-rare hamburgers because of food-safety concerns, so the protein dries out," Drescher says. "The mushroom hydrates it, plus you get this umami factor that's not as present otherwise." Umami is the savory "fifth taste" (in addition to sweet, salty, bitter and sour) that is abundant in foods like soy sauce and ripe tomatoes; it's part of what makes a burger delicious. The data have already convinced some huge food-service companies to buy less meat. London-based Compass, which has a $14 billion North American operation, reduced red meat purchases by 10 percent in the fall of 2015, the first year that it began following Menus of Change principles.

### STEALTH-HEALTH YOURSELF

Today, motivation-focused health interventions are moving outside labs and restaurant kitchens. On the "stealth exercise" front, there's GirlTrek, a nonprofit that encourages African-American women to form groups in their neighborhoods for daily walks. "This is not a fitness organization, this is a campaign for healing. … We walk to heal our bodies, inspire our families and to reclaim the streets of our neighborhoods," the organization's mission statement reads in part. So far, 67,000 women and girls have pledged to walk regularly in their neighborhoods.

Robinson and Gardner have even snuck stealth-health elements into their own lives. Gardner leads a weekly volleyball game at the medical school that's been going since 2001. Yes, it's exercise, he says, but the players are mostly there to have fun. (The net they use was purchased with "employee morale" funds from the prevention research center.)

As for Robinson, after moving to San Francisco, he started taking public transportation and joined Stanford's Commute Club, which gives financial incentives to employees who reduce their car trips to campus. He's not quite sure what motivated him — maybe the money he saved, maybe the environmental benefits, maybe the fact that he really hated being stuck in his car. One thing's for sure, though, Robinson says: "I don't take the train for my health. But as a side effect, I noticed that after I stopped driving, my HDL went up by 10 points." He attributes at least part of the rise in his "good cholesterol" to his daily walks to and from the train, which provide a stealthy bit of exercise he wouldn't otherwise get. "That," he says, "is pretty cool." **SM**

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At what cost?

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what they have in an amazing way," he says. It is much harder to get products manufactured in a consistent way in India, venture capital is limited, clinical trials are hard to carry out and patents aren't always respected — all of which change the way fellows think about how to get their innovative ideas to patients.

Yock hopes that exposing fellows to other ways of thinking about innovation will improve their own chances in global markets.

### TECHNOLOGY MATTERS

Brinton says that in designing the fellowship program to meet today's market, here and internationally, the goal isn't just to help bright young people start companies. It's to help patients.

"At Stanford we are training people to be leaders in their fields," he says. "We train the physicians how to use technology that saves people's lives, and now we are training them in how to develop new inventions with the same goal — to better care for patients."

Brinton and Yock see medical-technology innovation as a discipline that has a natural home in a university setting. It's a complex and interdisciplinary set of skills that needs the broad intellectual resources of a campus and medical system to develop fully.

Mastering those skills creates innovators who can go on to have large-scale impact on patient care. Krummel says that as a surgeon he can do quite a bit of good, one patient at a time. "Teaching is multiplicative. My students can develop a new technology that is used all over the world," he says. "I could never personally do that much good on my own.

"That's a great reason to get up in the morning and go to work. In the end, given that we are all consumers of health care, anything that can be better, safer, cheaper — there's a public good there." **SM**

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**FEATURE**

Inflammation implication

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So-called M1 macrophages, on the other hand, are pugnacious, proactive and perhaps a bit paranoid. They blow the whistle on infectious pathogens or suspected tumor cells, recruiting other types of immune cells to the scene and squirting out pro-inflammatory signaling proteins that act both locally and systemically to ramp up the entire immune system to high-alert status. They also attack the pathogens or tumor cells directly.

Cardiovascular catastrophes — heart attacks and strokes — now appear to be tripped off by macrophages, the very immune cells charged with clearing plaques.

The buildup of dead cells and fatty-plaque components in atherosclerotic lesions should

normally be prevented by M2 macrophages' garbage-disposal service. But with age, their job performance falls off, while M1-types' activity ramps up. M1 macrophages' unremitting secretion of inflammatory substances can render plaques brittle, increasing the risk that a chunk will break off and form a clot that can trigger a heart attack or a stroke.

In a study published in *The Journal of Experimental Medicine* in February, Weyand found that the macrophages of coronary artery disease and stroke patients have a defect that turns them into not only M1s, but sugar-holic M1s to boot. They slurp up too much glucose from the blood, ratcheting their internal metabolic activity into overdrive. That, in turn, prods them into churning out buckets of a pro-inflammatory substance called IL-6, which brings still more angry immune cells to atherosclerotic lesions and perpetuates an inflammatory vicious circle.

In a series of experiments with potential therapeutic implications, Weyand and her colleagues showed that several different biochemical interventions could prevent macrophages' sugar-high-crazed inflammatory rampage in atherosclerotic lesions. The discovery could give rise to new ways of curing or preventing cardiovascular disease. Tests in mice indicate, for example, that it may be possible to design compounds that prevent defective macrophages from hyper-metabolizing glucose, or that moderate the inflammation-inducing effects of that hyper-metabolism.

Weyand's got nothing against macrophages, per se. "We can't live without them," she says.

Leeper likewise bears no grudge. "Macrophages set out with good intentions," he says. "We think they're trying to do the right thing with atherosclerotic plaque, but they choke on it instead."

In a study published in July in *Nature*, Leeper discovered an important reason dead cells pile up in atherosclerotic lesions to begin with: They sport a "don't eat me" signal, in the form of a cell-surface protein called CD47 that deters macrophages' voracious salvos. Irving Weissman, MD, professor of pathology and of developmental biology, and his colleagues have identified high levels of CD47 on cancer cells as a strategy that tumors use to evade immune attack.

Leeper's study found, serendipitously, that CD47 is overexpressed on the dying and dead cells in atherosclerotic plaques, obstructing macrophages' efforts to clear those cells from the scene. When he and his associates blocked this protein with anti-CD47 antibodies, they were able to counter plaque buildup and vulnerability to rupture in several different mouse models of atherosclerosis. Many mice even experienced regression of their plaques.

His team also found that TNF-alpha, like IL-6 an important pro-inflammatory substance, promotes elevated CD47 expression in dying cells in atherosclerotic tissue. Rendered inedible, the cells die in place and secrete still more TNF-alpha-inducing substances. And so forth.

Leeper notes that people with autoimmune disorders characterized by abundant systemic inflammation, such as rheumatoid arthritis or lupus, are at elevated risk for premature cardiovascular disease. But patients taking anti-TNF drugs for rheumatoid arthritis or lupus have fewer heart attacks and strokes than would otherwise be expected for these patients.

It's already known that aspirin, a nonsteroidal anti-inflammatory drug, lowers cardiovascular risk, and that statin drugs — vaunted for cutting cholesterol production — also exert a pronounced anti-inflammatory effect. But the fact that each of these drugs works by multiple mechanisms makes it hard to prove that it is specifically their anti-inflammatory properties that are producing cardiovascular benefits. Two national trials are enrolling more than 25,000 patients at heightened risk of cardiovascular events to explore whether medications whose effects are known to work only through anti-inflammatory mechanisms can prevent heart attacks and strokes.

In addition, CD47-blocking antibodies are now being administered to cancer patients in early-stage clinical trials underway at Stanford and the University of Oxford. If those antibodies prove safe, they'll be strong candidates for repurposing to combat cardiovascular disease.

Low-grade chronic inflammation is implicated in not just cardiovascular conditions but cancer, Alzheimer's and Parkinson's, Type 2 diabetes and both rheumatoid arthritis and osteoarthritis — age-associated diseases all, with at least one affecting most people age 65 or older. That age — one the great majority of people born in industrialized countries can expect to reach — describes one in seven Americans now and will encompass about one in five in 2030, according to the U.S. Census Bureau. So many leaky faucets spell not only big bills to come, but an inflammaging-fueled flood headed our way. If researchers can find the factors underlying this flood, there's hope that the right washers and wrenches can stop the drip and help us all live to a healthy old age. **SM**

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